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A Protocol for Assessing Subtraction Errors of Arterial Spin-Tagging Perfusion Techniques in Human Brain

Martin N. Yongbi, Charlene X. Tan, Joseph A. Frank, and Jeff H. Duyn*

A protocol for assessing signal contributions from static tissue (subtraction errors) in perfusion images acquired with arterial spin-labeling (ASL) techniques in human brain is proposed. The method exploits the reduction of blood T_1 caused by the clinically available paramagnetic contrast agent, gadopentetate dimeglumine (Gd-DTPA). The protocol is demonstrated clinically with multislice FAIR images acquired before, during, and after Gd-DTPA administration using a range of selective inversion widths. Perfusion images acquired postcontrast for selective inversion widths large enough (threshold) to avoid interaction with the imaging slice had signal intensities reduced to noise level, as opposed to subtraction errors manifested on images acquired using inversion widths below the threshold. The need for these experiments to be performed in vivo is further illustrated by comparison with phantom results. The protocol allows a one-time calibration of relevant ASL parameters (e.g., selective inversion widths) in vivo, which may otherwise cause subtraction errors. Magn Reson Med 43: 896–900, 2000. Published 2000 Wiley-Liss, Inc.†

Key words: perfusion; subtraction error; slice profile; Gd-DTPA

Imaging of tissue perfusion using arterial spin labeling relies on some method for distinguishing the perfusion signal from stationary tissue by means of subtraction of images between a tag and a control state (1–8). Since the perfusion signal is relatively small (~1% of M_o (2,8)), contributions from static tissue (or subtraction error) following subtraction of the tag from the control image must be kept to an absolute minimum to avoid significant quantitative errors. In pulsed labeling methods (e.g., EPISTAR (3), FAIR (4,5,8), QUIPPS (7), UNFAIR (6)), the subtraction errors arise primarily because of interactions caused by imperfections in the imaging and selective inversion pulse profiles (8,9,13–15). The degree of this interaction (hence the subtraction error) largely depends on the sharpness of the inversion profile, which is also significantly dependent on the T_2 of the medium. This slice profile dependency on T_2 and its effects on spin-tagging perfusion measurements has recently been demonstrated by Frank et al. (9). Generally, media with longer T_2 relaxation times produce sharper slice profiles. To date, experiments designed to assess subtraction errors have primarily employed water- or gel-based phantoms. Since the relaxation times are generally longer in phantoms (coupled with reduced magnetic susceptibility), slice profiles in these media are generally sharper. Additionally, since pulse profiles are generally worse in media with flow (16–18), the slice profile differences between normal brain where there is flow compared to phantoms (no flow) *may be* accentuated by this effect. Other potential contributing effects to differences between the profiles include magnetic susceptibility variation and motion, e.g., from brain pulsation.

In the FAIR (4,5) or uninverted FAIR experiments (6), the selective inversion thickness must be increased relative to the imaging slice to avoid subtraction errors. The latter requirement warrants the calibration of the selective inversion thickness in order to avoid residual subtraction errors during brain perfusion studies. Calibrations based on phantoms can underestimate the required slab thickness due to differences in the profiles between the two media. Recent studies also suggest discrepancies in subtraction errors obtained using similar inversion widths in the two media may be accentuated by differences in magnetization transfer (9) and radiation damping (10) between the two media. Therefore, it would be beneficial to perform these calibrations in more realistic media if these errors are to be minimized.

The purpose of this study was to develop a protocol to allow assessment of subtraction errors of arterial spin-labeling perfusion techniques in human brain. This approach takes advantage of the significant T_1-reducing effect of blood water by gadopentetate dimeglumine (Gd-DTPA), which causes loss of the magnetic label during transit to the imaging slice. The protocol is demonstrated in human brain by means of FAIR perfusion images acquired pre- and post-Gd-DTPA using a range of selective inversion slab widths, and compared with the results obtained using a standard phantom.

METHODS

Basis of Technique

Among other factors (e.g., flow rate, T_1), the signal (ΔM) obtained using FAIR and other related techniques (1–3,6,7) largely depends on the degree that the spins in blood are inverted at the capillary exchange site. An estimation of ΔM which also accounts for arterial transit times (τ_a) has been presented elsewhere (8), and is given by:

$$\frac{\Delta M(t)}{M_0} = \begin{cases} 0 & (for\ 0 < t < \tau_a) \\ -\dfrac{2.f}{\lambda} \cdot e^{-\frac{1}{T_{1a}} \cdot t} \left(\dfrac{1 - e^{-\delta R \cdot (t - \tau_{a,n})}}{\delta R} \right) & (for\ \tau_a < t < \tau_d) \end{cases}$$

M_o is the equilibrium magnetization, f is the cerebral blood flow, λ is the partition coefficient of brain water, $\delta R = R_1 - R_{1a}$ with R_1 and R_{1a} being the relaxation rates of brain and arterial water, respectively. τ_d the time for the trailing

Laboratory of Diagnostic Radiology Research, Clinical Center, National Institutes of Health, Bethesda, Maryland.

*Correspondence to: Jeff H. Duyn, Ph.D., Laboratory of Diagnostic Radiology Research, CC, NIH, Building 10, Room B1N256, 9000 Rockville Pike, Bethesda, MD 20892. E-mail: Jhd@helix.nih.gov

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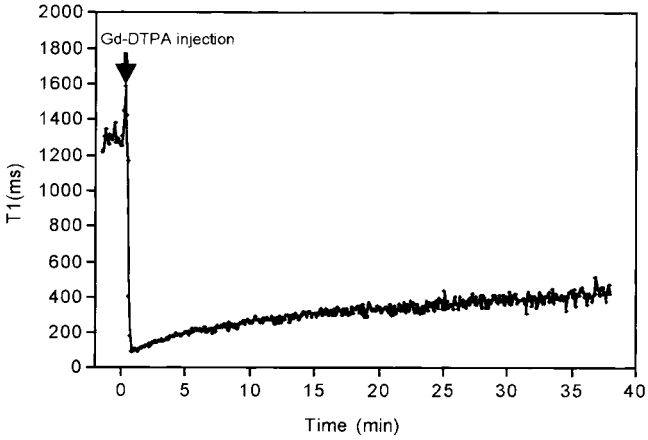

FIG. 1. Continuous T_1 measurement of human blood (in the sagittal sinus) using a two-point inversion recovery single-shot spiral sequence, showing significant reduction of blood T_1 following a double dose of Gd-DTPA. Global inversion was achieved using the body coil and signal reception with a 3 cm surface coil. Data is shown 2 min before and 38 min post Gd-DTPA.

edge to reach the capillary site, and $\tau_{a,n}$ is the transit time for the nth slice. From the preceding expression, ΔM can be seen to decrease exponentially with T_{1a}. T_{1a} was reduced by i.v. administration of a double dose (0.2 mmol/kg at 1.0 cc/min) of Gd-DTPA (MAGNEVIST; Berlex Laboratories, Cedar Knolls, NJ) to four healthy volunteers. Preliminary measurements performed during the course of this study indicate this dose to reduce T_{1a} from ~1300 ms to ~100 ms (see Fig. 1). The shortened T_1 of blood results in a theoretical reduction of ΔM from ~1% to <0.1% of M_o, suggesting that the postcontrast FAIR signal should be reduced to noise levels.

EXPERIMENTS

All data collection was performed on a 1.5 T system equipped with shielded gradients with a slew rate of 120 T/m/s (General Electric, Milwaukee, WI). A quadrature head coil was used for signal excitation and reception. The FAIR sequence was based on the fast spiral-readout technique (8). For selective and nonselective adiabatic inversion, we used the C-FOCI adiabatic inversion pulse (11,12), recently demonstrated to provide better overall perfusion labeling in view of its much better inversion profiles (13–15,19).

A series of multislice baseline FAIR experiments was performed in four healthy volunteers (age range: 23–39 years). FAIR imaging parameters were: matrix = 64 × 64, FOV = 24 cm, recovery-delay = 3 sec, TE = 8 ms, spiral-readout time = 22 ms, slice thickness = 5 mm (10 slices), TR = 35 ms, TI = 1.5 sec, 10 pairs of selective (tag) and nonselective (control) inversion recovery images acquired in an interleaved manner. For each volunteer (n = 3) the selective FOCI width for the FAIR experiment was varied from 50 mm to 100 mm. The latter procedure was repeated 30 sec following Gd-DTPA administration. In the fourth healthy control, continuous FAIR raw data was collected for 30 min, during which a double dose (0.2 mmol/kg) of Gd-DTPA was administered at the start of the fifth min. For the latter measurement, a selective FOCI width of 80 mm was used, as this corresponds to the minimum width for which the subtraction error indicated in an earlier study was <0.1% of M_o. Other measurement parameters were the same as for the above experiments. All clinical studies were performed as part of an approved intramural review board protocol at the National Institutes of Health, Bethesda, Maryland.

RESULTS AND DISCUSSION

Figure 2 shows multislice baseline FAIR images acquired from a healthy volunteer using selective FOCI width of 50 mm (Fig. 2a–i), and 80 mm (Fig. 2a-ii). An unusually higher perfusion signal can be seen to characterize the outermost two slices for the series of images acquired with a 50 mm FOCI width. The latter is largely due to interactions between the edges of the inversion and imaging pulse profiles, which results in contribution from static tissue. The FAIR contrast and signal intensity of the outermost two slices progressively approached those of the central six slices as the selective FOCI width was progressively increased. This observation was confirmed by plotting the FAIR signal intensity (ΔM), integrated over all 10 slices, vs. selective inversion width (Fig. 2b). The total ΔM was found to decrease initially at a faster rate with increasing inversion slice width. This trend is expected since the static tissue signal component in the perfusion slices reduces with increase in the selective inversion width. The signal approaches a plateau for selective inversion widths = 80 mm, indicating substantial elimination of the static tissue component from the FAIR images. This conclusion is validated in Fig. 2a-iii and 2a-iv, which depict FAIR images (same slices as in Fig. 2a-i, 2a-ii) acquired postcontrast administration with selective inversion widths of 50 mm and 80 mm, respectively. The FAIR images acquired with the 50 mm width manifested significant residual subtraction error compared with the image acquired using an 80 mm inversion width, for which there is evidently no residual static signal. Given the loss of arterial tag which occurs post-Gd-DTPA caused by the reduced blood T_1 (Fig. 1), the absence of FAIR signal in the latter FAIR image implies the subtraction errors were primarily caused by interactions between the RF pulses. Because of pulsation, the post-Gd-DTPA FAIR signal in the sagittal sinus randomly fluctuated between positive and negative values, even for inversion widths of up to 100 mm. Phantom subtraction images acquired with FOCI slab thickness of 50 mm and 70 mm are shown in Fig. 2a-vi and 2a-vii, respectively. It can be seen from this figure that the phantom subtraction error was reduced to noise at a selective FOCI thickness of 70 mm, as opposed to 80 mm for the brain study (Fig. 2a-iv).

To estimate the subtraction error as a function of selective FOCI width, the post-Gd-DTPA FAIR signal was integrated over all 10 slices and plotted against the FOCI width (Fig. 3). The corresponding data obtained from an agar gel phantom with T_1/T_2 ~1000/80 ms (consistent with that found in gray matter at 1.5 T) is plotted on the same graph. For both cases, the subtraction error decreased with increasing FOCI slab width as the interaction between the

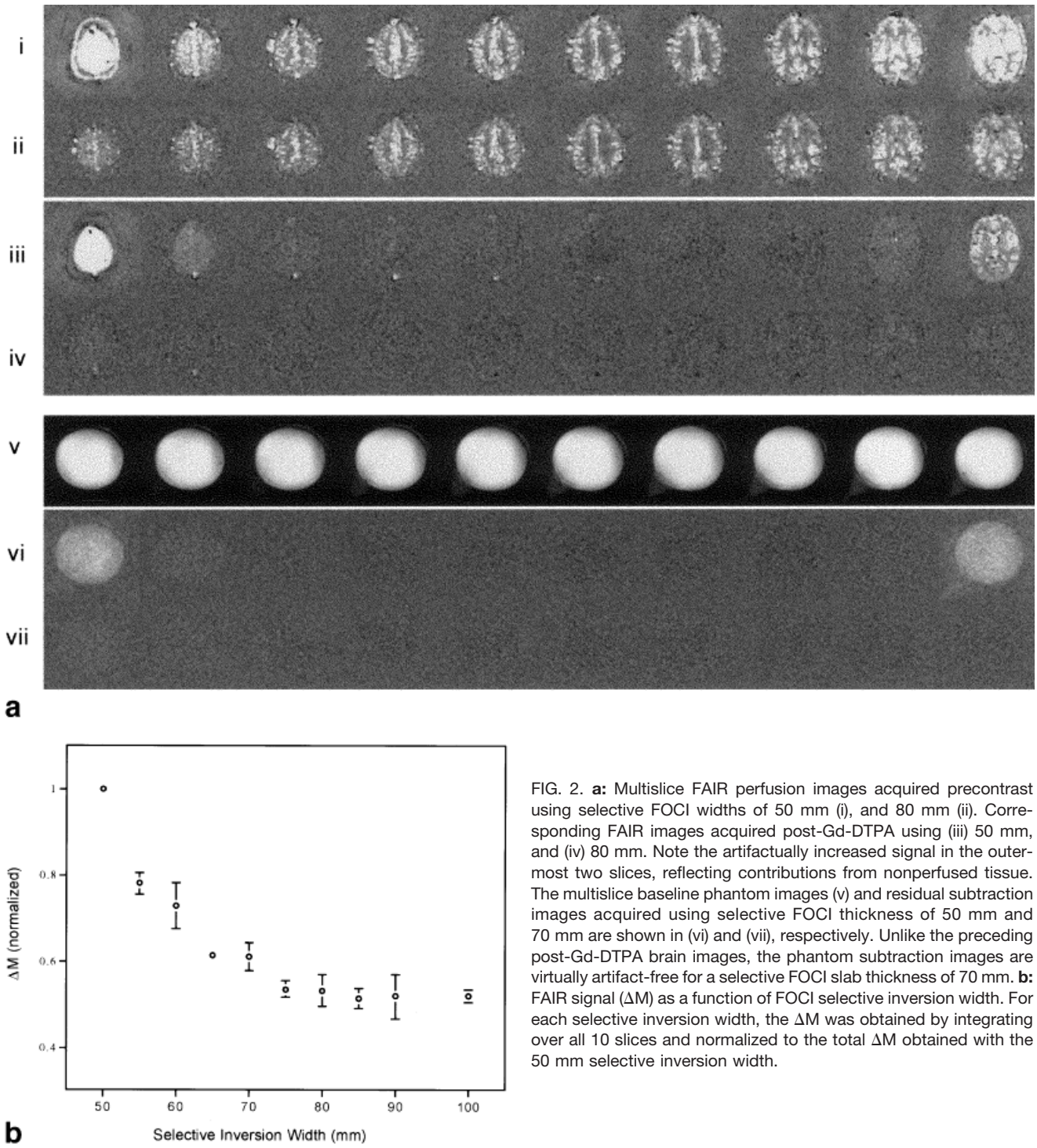

FIG. 2. **a:** Multislice FAIR perfusion images acquired precontrast using selective FOCI widths of 50 mm (i), and 80 mm (ii). Corresponding FAIR images acquired post-Gd-DTPA using (iii) 50 mm, and (iv) 80 mm. Note the artifactually increased signal in the outermost two slices, reflecting contributions from nonperfused tissue. The multislice baseline phantom images (v) and residual subtraction images acquired using selective FOCI thickness of 50 mm and 70 mm are shown in (vi) and (vii), respectively. Unlike the preceding post-Gd-DTPA brain images, the phantom subtraction images are virtually artifact-free for a selective FOCI slab thickness of 70 mm. **b:** FAIR signal (ΔM) as a function of FOCI selective inversion width. For each selective inversion width, the ΔM was obtained by integrating over all 10 slices and normalized to the total ΔM obtained with the 50 mm selective inversion width.

imaging and inversion RF profiles declines. However, the subtraction error decreased at a faster rate in the phantom. In the healthy control brain studies performed so far (n = 4), subtraction errors were consistently found to be = 0.1% of M_o for selective FOCI width above 80 mm, as opposed to 70 mm indicated by the phantom study. A slight drawback of the proposed method is its invasiveness. However, the high reproducibility of the technique implies that it only be applied once for calibrating and setting up perfusion sequence parameters.

The time course of the FAIR signal acquired before, during, and after Gd-DTPA from one healthy control, averaged over all 10 slices for each selective and nonselective IR pair, is shown in Fig. 4. For this study, ΔM declined to the noise level within ~20 sec following the onset of Gd-DTPA infusion. As seen in the figure, the average ΔM remained within noise for at least 25 min following the initial decline. In fact, multislice ΔM images acquired 35 min postcommencement of Gd-DTPA infusion indicated signal levels <0.1% of M_o, indicating a relatively

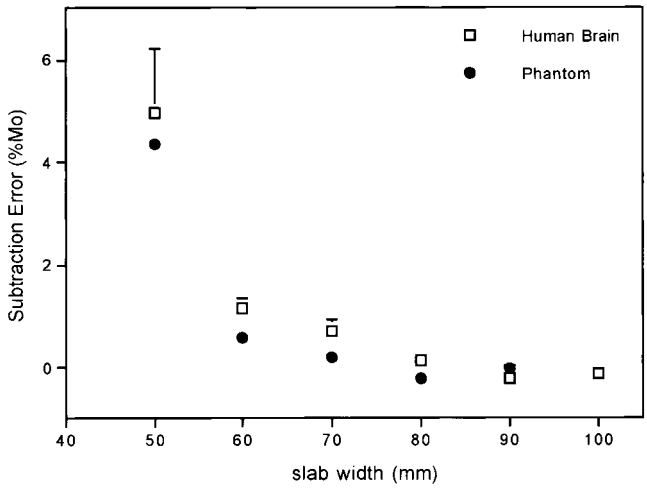

FIG. 3. Plot of subtraction error ±SD (n = 3) vs. inversion slab width for both phantom and human brain studies. For inversion widths below 80 mm, phantom subtraction error is consistently lower than for the in vivo case. The rather high standard deviation of the first data point may be due to large variance in the time required for equilibration of the gadolinium contrast within the vascular system.

slow clearance rate of the contrast agent from the micro vasculature. This slow clearance allows sufficient time (>30 min) for calibration of relevant sequence parameters, such as the inversion threshold voltage and selective widths.

A potential problem with the protocol may arise if leakage of the Gd-DTPA into tissue space occurs. This leakage will reduce tissue T_1 and, because the subtraction errors are relatively small, this T_1 reduction can cause an artificial reduction in the subtraction error. However, signal intensity and T_1 measurements of gray and white matter performed pre- and postcontrast injection indicated no significant changes in these parameters. A similar observation was recently reported in normal rat brain by another group (21), and can attributed to the protective effects of the intact blood–brain barrier.

Overall, our results suggest the need for such assessments to be performed directly on brain tissue. It should be noted that the calibrated FOCI widths are specific for typical parameters used in this study. Small differences in inversion widths may be observed in studies employing FOCI RF of slightly different design, particularly in situations where FOCI pulses of different bandwidths (BW) and scaling factors (*A(t)* (11–13)) are employed.

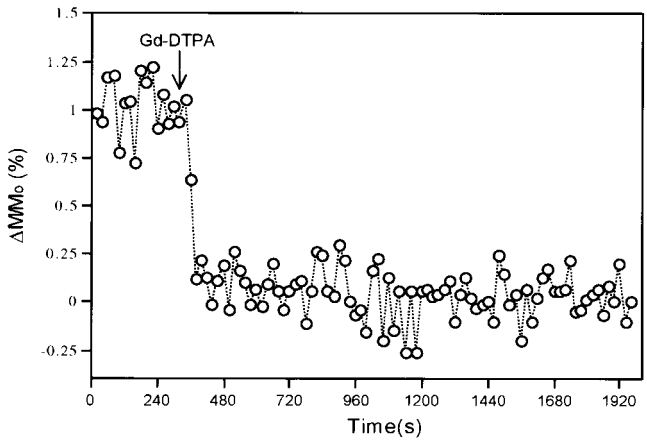

FIG. 4. FAIR signal integrated over all 10 slices as a function of time, pre- and post-Gd-DTPA injection.

CONCLUSIONS

We have demonstrated a protocol for assessing static tissue subtraction errors in human brain perfusion studies employing arterial spin tagging. The approach takes advantage of the rapid loss of the tag due to an enhanced blood relaxation rate following Gd-DTPA administration. Since this protocol relies on assessments performed directly on brain tissue, it eliminates potential sequence calibration errors caused because of the intrinsic differences between water/gel phantoms and tissue, e.g., relaxation, susceptibility, flow, magnetization transfer, and radiation damping. Although demonstrated using FAIR, the proposed protocol can readily be applied for evaluating subtraction errors of other arterial spin-tagging sequences.

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REFERENCES

1. Detre JA, Leigh JS, Williams DS, Koretsky AP. Perfusion imaging. Magn Reson Med 1992;23:37–45.
2. Ye FQ, Pekar JJ, Jezzard P, Duyn JH, Frank JA, McLaughlin AC. Perfusion imaging of the human brain at 1.5T using a single-short EPI spin tagging approach. Magn Reson Med 1996;36:219–224.
3. Edelman RR, Siewert B, Darby DG, Thangaraj V, Nobre AC, Mesulam MM, Warach S. Qualitative mapping of cerebral blood flow and functional localization with echo-planar MR imaging and signal targeting with alternating radio frequency. Radiology 1994;192:513–520.
4. Kwong KK, Chesler DA, Weisskoff RM, Donahue KM, Davis TL, Ostergaard L, Campbell A, Rosen BR. MR perfusion studies with T_1-weighted echo planar imaging. Magn Reson Med 1995;34:878–887.
5. Kim S-G. Quantification of relative cerebral blood flow change by flow sensitive alternating inversion recovery (FAIR) technique: application to functional mapping. Magn Reson Med 1995;34:293–301.
6. Helpern JA, Branch CA, Yongbi MN, Huang NC. Perfusion imaging by un-inverted flow-sensitive alternating inversion recovery (UNFAIR). Magn Reson Imaging 1997;31:454.
7. Wong EC, Buxton RB, Frank LR. Quantitative imaging of perfusion using a single subtraction (QUIPSS and QUIPPS II). Magn Reson Med 1998;39;702–708.
8. Yang Y, Frank JA, Hou L, Ye FQ, McClaughlin AC, Duyn JH. Multislice imaging of quantitative cerebral perfusion with pulsed arterial spin labeling. Magn Reson Med 1998;39:825–832.
9. Frank LR, Wong EC, Buxton RB. Slice profile effects in adiabatic inversion: application to multi-slice perfusion imaging. Magn Reson Med 1997;38:558–564.
10. Zhou J, Mori S, van Zijl PCM. FAIR excluding radiation damping (FAIRER). Magn Reson Med 1998;40:712–719.
11. Ordidge RJ, Wylezinska M, Hugg JW, Butterworth E, Franconi F. Frequency offset corrected inversion (FOCI) pulses for use in localized spectroscopy. Magn Reson Med 1996;36:562–566.
12. Payne GS, Leach MO. Implementation and evaluation of frequency offset corrected inversion (FOCI) pulses on a clinical MR system. Magn Reson Med 1997;38:828–833.
13. Yongbi MN, Branch CA, Helpern JA. Perfusion imaging using FOCI RF pulses. Magn Reson Med 1998;40:938–943.

14. Yongbi MN, Yang Y, Frank JA, Duyn JH. Multi-slice MR perfusion imaging in human brain using FOCI RF pulses. In: Proc ISMRM, 7th Annual Meeting, Philadelphia, 1999. p 1841.
15. Yongbi MN, Yang Y, Frank JA, Duyn JH. Multi-slice MR perfusion imaging in human brain using the C-FOCI inversion pulse: comparison with hyperbolic secant. Magn Reson Med 1999;42:1099–1105.
16. Lewis DP, Tsui BMW, Moran PR. Velocity sensitivity of slice-selective excitation. Magn Reson Imaging 1998;16:907–916.
17. Gao JH, Gore JC. Effects of slow flow on slice profile and NMR signal in fast imaging sequences. Phys Med Biol 1994;39:1489–1500.
18. Yuan C, Gullberg GT, Parker DL. The solution of Bloch equations for flowing spins during a selective pulse using a finite difference method. Med Phys 1987;14:914–921.
19. Pell GS, Thomas DL, Calamante F, Howseman AM, Williams SR. Measurement of perfusion using arterial spin tagging with the FOCI pulse. In: Proc ISMRM, 6th Annual Meeting, Sydney, Australia, 1998. p 1190.
20. Landis CS, LI X, Coderre JA, Micaa PL. Towards direct MRI determination of the thermodynamic (interstitial) CR concentrations in tumors following bolus injection. In: Proc ISMRM, 7th Annual Meeting, Philadelphia, 1999. p 1181.